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10/586,255	09/11/2006	Peter Ghosh	47-233	4757

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EXAMINER	
HADDAD, MAHER M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,255	GHOSH, PETER	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *29-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/11/06&7/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-36 are pending.

2. Applicant's election of Group I, claims 1-36 directed to a method of preventing the onset of a harmful immune response or at least one symptom thereof in a connective tissue of an animal to an antigen, comprising administering a composition comprising one or more GAG-peptide complex, wherein at least one GAG-peptide complex comprises 2 or 3 GAG chains and inflammation and cartilage as the species, filed on 8/28/08, is acknowledged. . Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 29-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1-28 are under examination as they read on a method of preventing the onset of a harmful immune response or at least one symptom thereof in a connective tissue of an animal to an antigen, comprising administering a composition comprising one or more GAG-peptide complex, wherein at least one GAG-peptide complex comprises 2 or 3 GAG chains and inflammation and cartilage as the species.

5. Applicant's IDS, filed 9/11/06 and 7/17/06, is acknowledged, however, the WO 94/2889 and DE 857,389 references, filed 9/11/06, were crossed out because the `889 document was not found and the English translation of the `389 document was not found. Applicant is invited to produce such documents. Further, the Parthasarathy et al reference filed 7/17/08 was crossed out because it is a duplicate of the same reference filed 9/11/06.

6. Claim 1 is objected to because "GAG" should be spelled out.

7. 35 U.S.C. § 101 reads as follows:

> *"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".*

8. Claims 15-28 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

10. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-28 provide for the use of GAG-peptide complex, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

B. The recitation "a prophylactic protocol" in claims 4 and 18 is ambiguous; it is clear what protocol is contemplated.

C. The recitation "one or more GAG-peptide complex, wherein at least one GAG-peptide comprises 2 or 3 GAG chains" is ambiguous, it is not clear what other GAG-peptide complex are encompassed by the claim.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing arthritis in rate type II collagen induced arthrsits (CIA) and rat adjuvant arthritis (AIA) model comprising orally administering a GAG-peptide complex comprises 2 Chs chains, CaP, does not reasonably provide enablement for methods of claims 1-28. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses the use of CIA and AIA as a model for the prevention and treatment of arthritis using oral administration of CaP (GAG complex comprises 2 ChS) (see pages 52-55). The specification on page 56, lines 14-17, discloses that oral administration of Cap or the GAG-p complex alone to rats for 7 days before inducing CIA suppressed the manifiestations of the disease for up to 18 days post antigen inoculation. On page 57, lines 12-18, the specification discloses that by day 18 CaP at 20 mg/kg was found to be less effective than GAG-P as

suggested by the extent of rear paw swelling (Fig.13). While the GAG-peptide prepared from cartilage by limited hydrolysis with sodium hydroxide (GAG-PLH) was found to be equivalent to GAG-P in the rat CIA model when given prophylatically at 200 mg/kg. The specification on page 57, lines 19-22, discloses that both Cap and GAG-P were active in preventing disease development when used prophylatically in the rat AIA model (Fig. 15). However, a stronger effect of GAG-P was indicated on Day 18 in terms of front paw inflammation, although Cap at 200 mg/kg demonstrated higher potency in the other parameters (fig. 16).

However, US. Patent 7,371,820 teaches in the Polycation(polylysin)-Hyaluronan complex (PC) arthritis model a 300 mg/ml oral administration of CaP daily for 14 days beginning 7 days before PC injection were statistically significant ($p<0.05$) for the prevention protocol. (see col., 35, lines 8-11). Claim 14 claims the administration of an amount of about 10-20 mg/kg. Further, Ghosh et al (Infl ammopharmacology 14 (2006) 161–168) teaches that Calcium Peptacan exhibited minimal anti-arthritic activity in the AIA model at 20 mg/kg but was active at the higher dose of 200 mg/kg (Fig. 6). Surprisingly GAG-P was active at 20 mg/kg although it failed to significantly control front paw inflammation (Fig. 6) (see page 165, 1st col., top ¶). Applicant claims a method of preventing inflammation (see claim 2 for example).

Ghosh et al teach that CaP was also active in preventing arthritis onset at 3.3, 10 or 20 mg/kg in the rat CIA model using the toleragenic protocol. It was only active at 20 and 200 mg/kg in the CIA prophylactic protocol. GAG-P was active in the CIA toleragenic protocol at 20 mg/kg. The efficacy of CaP in the rat AIA model was less than in the CIA model. These findings lead us to suggest that oral CaP could be used as a disease-modifying anti-arthritic drug (see abstract). Ghosh et al teach that how the CaPeptacan induces tolerance/immuno-unresponsiveness has yet to be clarified (see page 166, left col., 2nd full ¶). However, it is not clear which of the three animal models represent prevention in animal including human arthritis.

Claims 7 and 21recite "induces tolerance in the animal to the antigen". However, Ghosh et al teach that how the CaPeptacan induces tolerance/immuno-unresponsiveness has yet to be clarified (see page 166, left col., 2nd full ¶). Further, claims 1 and 15 provide no requirement for the specific antigen, but rather claiming GAG-peptide complex comprises 2 or 3 chains that induces any antigen tolerance in the animal in the prevention of the onset of a harmful immune response.

Claims 10 and 24 recites at least one connective tissue derived polypeptide, it is not clear what polypeptide is being claimed. It is not clear what connective tissue derived polypeptide would lead to the prevention of onset of a harmful immune response. The specification provides no guidance on what connective tissue derived polypeptide would be use in the claimed method.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

14. Claims 1-11, 13, 15-26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/28889.

The `889 publication teaches and claims a method for treatment of osteoarthritis comprising administering to an osteoarthritis-affected patient the glycosamingoglycan mimic and contacting an osteoarthritis-diseased tissue of the patient with an effective amount of the glycosaminoglycan mimic so that the osteoarthritis is at least partially alleviated (see published claim 21). A mothod for the treatment of osteoarthritis comprising administering to an osteoarthritis-affected patient the purified glycosaminoglycan or proteoglycan species so that the osteoarthritis is at least partially alleviated (see published claim 23), wherein the hard tissue is cartilage (see published claim 23 and page 11, lines 15-20). The `889 publication further teaches that the lower limit for a GAG molecule of the invention will be one consisting of 2-3 monosccharide units (see page 14, lines 2-3 in particular). The `889 publication teaches that the components of the invention serve to alleviate and prevent a prevalent human disease such as osteoarthritis (OA) (see pages 27-28, bridging ¶). The `889 publication teaches that the components of the invention can be prepared as injectable formulations (see page 28, lines 16-25).

Claim 10 is included because the reference GAG-peptide contains a connective tissue derived polypeptide.

The reference teachings anticipate the claimed invention.

14. Claims 1-12, 15-26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 2003/062279 A1 (IDS reference).

The `279 publication teaches and claims the use of CAP (33.7 kDa) and H2OP (46.1 kDa) GAG-peptides comprising 2ChS cains and 3 ChS chains, respectively (see page 42, lines 21-30), for the treatment, protection and restoration of connective tissues in inflammatory and degenerative disorders such as rheumatoid arthritis and osteoarthritis in any of their multiple forms or other

degenerative conditions in mammal (see abstract, claims 14, 16-27, page 46-47, bridging ¶ and page 33 under Experimental Protocols). The `279 publication teaches that the 100, 200 or 300 mg/kg was administered orally to rabbits in which monoarticular proliferative arthritis had been induced by the intra-articular injection of a PC-complex. The preparations were given daily for 7 days before arthritis was inducted and daily for 7 days thereafter (see page 33 Experimental Protocols and page 46, lines 22-27).

Claim 10 is included because the reference GAG-peptide contains a connective tissue derived polypeptide.

The reference teachings anticipate the claimed invention.

15. Claims 1-12, 15-26, and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 7,371,820 B2 (Ghosh).

The `820 patent teaches the use of Calcium Peptacan (CaP)GAG-peptide on the joint tissues of the rabbit arthritis model, it was also found to suppress the levels of both neutrophils and mononuclear cells circulating in the blood of the arthritic animals (FIGS. 34 and 35). While these blood borne white cells serve as an important vanguard in the immune defense against invading pathogens, once activated, as occurs in inflammatory states such as rheumatoid arthritis (cartilage)and osteoarthritis (cartilage)they provide an ongoing source of destructive proteinases (preventive), oxygen derived free radicals and pro-inflammatory cytokines all of which contribute to the initiation and perpetuation of the disease process (see col., 35, line 64 to col., 36, line 45).

The `820 patent further teaches that the in vitro stimulation of the biosynthesis of HA by synovial fibroblasts derived from joints of humans with osteoarthritis by CaP was also demonstrated to occur in vivo using an animal model of arthritis. In these latter experiments ChS at 300 mg/kg or CaP at 100, 200, or 300 mg/kg was administered orally to rabbits in which monoarticular proliferative arthritis had been induced by the intra-articular injection of a PC-complex. The preparations were given daily for 7 days before arthritis was inducted and daily for 7 days thereafter. The results of these experiments are shown in FIGS. 30 and 31. Compared to the non-drug treated control group synovial fibroblasts from all animals in the CaP treated group showed higher synthesis of HA (FIG. 30), however, because of the inter-animal biological variation only the group receiving the dose of 300 mg/kg were statistically significant ($p<0.05$) relative to the non-drug-treated group (FIG. 31). If the comparison of HA stimulation by the treatments was based on their respective sulfated GAG content then CaP was more than 3X more active than ChS. Promotion of HA synthesis by synovial cells in arthritic joints would contribute to improved joint lubrication and a reduction of cartilage degradation (see col., 34, line 57 to col. 35, line 17).

The `820 patent teaches the administered 300 mg/kg (body weight) CaP orally daily for 14 days beginning 7 days before (prevention) PC injection (see Col., 25, lines 25-38).

The `820 patent teaches that the GAG-peptide in CaP contained 2 ChS chains while that in H2OP consisted of 3 ChS chains (see col., 31, lines 47-50 and table 2)).

Claim 10 is included because the reference GAG-peptide contains a connective tissue derived polypeptide.

The reference teachings anticipate the claimed invention.

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 12-14 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/28889 or WO 2003/062279 or 7,371,820, as applied to claims 1-11, 15-26 and 28 above.

The teachings of WO 94/28889, WO 2003/062279 and 7,371,820 have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of oral administration in claim 12, tropical administration in claims 13 and 27, and 10-20 mg/kg in claim 14.

It is clear that both the prior art and claimed method administer the same treatment to achieve the same results. It would be conventional and within the skill of the art to : (i) identify the exact dosage of 10-20 mg/ kg and (ii) determine an effective amount that does not GAG-peptide complex- induced tolerence . Further, it has been held that where the general conditions of a claim are disclosed in the prior art , discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. The determination of the optimal intervals of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment , the specific rout of administration and like factors within the knowledge and expertise of the medical practitioner.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claims 1-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims8-9 of U.S. Patent No. 7,211,648 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the `648 patents are species to the gerneic claim of the instant application. The `648 patent teaches and claims a method of providing at least one skin care benefit such as inflammation and swelling (harmful immune response or at least ones symptom thereof) to a subject in need thereof, the method comprising applying a topical composition comprising a connective tissue derived composition comprising one or more GAG-peptide complex in combination with a dermatalogically acceptable vehicle, wherein at least one GAG-peptide complex comprises 2 or 3 GAG chains (see patented claim 8). Or a method of using a topical composition comprising a connective tissue derived composition comprising one or more GAG-peptide complex in combination with a dermatalogically acceptable vehicle, wherein at least one GAG-peptide complex comprises 2 or 3 GAG chains for providing at least one skincare benefit or subdermal tissue benefit to a subject in need thereof (see patented claim 9). The `648 patent teaches that the

GAG-peptide complexes described herein were not only active in preventing inflammation and arthritis (cartilage) in animal models of arthritis when administered orally but were also active when applied topically to human subject (see col., 36, lines 16-20).

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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